March 21, 2005

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Division of Dockets Management
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket 2004D-0524
Draft Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information

Dear Madam or Sir:

Enclosed please find comments from GlaxoSmithKline, including general and specific comments for the Draft Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information. These comments are presented for consideration by the FDA. The general comments are presented first, with the specific comments presented in order by section and line number in the draft guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting the comments for this draft guidance by hardcopy. Therefore, you will receive this letter with two copies of comments.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S. Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

2004D-0524 C5

Section	Guidance Line	Comment	Rationale/Proposed Change
General	-	The *Draft Guidance for Industry: Drug Substance Chemistry, Manufacturing, and Controls Information* (12/2003) will also apply to ANDAs; there should be a reference to that (draft) guidance in this draft guidance.	
General	-	The draft guidance purports to offer general guidance on polymorphism in ANDAs but the discussion and rationale for what is proposed in the draft guidance focus exclusively on solid oral dosage forms and oral suspensions. This should be clarified in the Introduction; either make it exclusive to solid oral dosage forms and oral suspensions, or expand it to include other dosage units. (Additionally, this impacts the title which could be ANDAs: Pharmaceutical Solid Polymorphism in Oral Solid and Suspension Drug Products or ANDAs: Pharmaceutical Solid Polymorphism.)	Solid state form can be equally or even more important in other dosage units e.g. medications for inhalation, topical application, transdermal products and sterile parenteral suspensions. In some such cases it is not practical nor possible to demonstrate "bioavailability" or bioequivalence and in vitro studies may not be relevant. Hence, control of the solid state form of the active ingredient becomes all-important. Yet, no mention is made of these other product types in the proposed guidance. There is a risk therefore that the draft guidance will assume relevance to such presentations by default.
General	-	Lack of control of solid state in the API can lead to inadequate control in cases where new indications and modes of delivery are identified for a drug and where solid state form is more important than in the original product form.	

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		Removing the requirement for using the solid state form that is employed in the RLD may well lead to tests on the API that do not distinguish a new solid state form. This poses the risk that it will be incorporated in a medicinal product without any characterization or studies to explore impact on processing or finished product quality or performance. The potential consequence is unacceptable product at some stage during its life with risk to the patient. This comment is also germane to the footnote (no 7) on page 2. The diversity of solid state behavior, coupled with knowledge that is only accumulated from published sources means that an authoritative decision cannot be taken to "consider only those polymorphs likely to form during manufacture of the drug substance, manufacture of the drug product, or while the drug substance or drug product is in storage"	It is generally accepted that it is good quality practice to incorporate performance or quality assurance testing as early as possible in the process viz controls on input API, excipients, packaging, during processing and on intermediate product are more appropriate for assuring quality (if relevant) than tests on the Finished Product. Furthermore, there can be cases where assurance of performance or quality cannot be guaranteed by finished product testing. For instance, product stability may be influenced by solid state form, with quality falling below satisfactory levels during shelf life. As stability cannot usually be assessed at release the choice of a suitably stable polymorph can provide better assurance of product quality retention. Although sophisticated techniques to predict identify and characterize potential solid state forms are now more numerous, it is still not possible to categorically establish that all potential solid state forms are predicted by structural considerations, or identified in solid state screens. New forms can occur at all stages of a product's life cycle, not just during development.
I.	26-28	A large extent of the draft guidance would apply to NDAs as well. So much of the content is not specific to ANDAs but it is not currently found elsewhere in such detail.	
I.	44-48	Given the potential for impact of solid state form on product performance, the positioning of this already weak draft guidance as 'recommended' rather than 'required' is inappropriate .	

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II.	50-67	The definitions are not in keeping with current terminology in that polymorphs are generally recognized as crystalline solid state forms. In the context of the draft guidance, polymorphic forms include solvates. This is at odds with the *Draft Guidance for Industry: Drug Substance Chemistry, Manufacturing, and Controls Information* (12/2003) which contains: 'Identification of the physical form (e.g., polymorph, solvate, or hydrate) that will be used in the manufacture of the drug product." Clearly solvate and hydrate are distinct from polymorph.	Including true polymorphs, pseudopolymorphs, amorphous forms and solvates under the blanket terminology of "polymorphs" is at variance with established ways of describing solid state forms, is imprecise science and is likely to confuse. Regulatory guidances should employ correct descriptive terminology and there should be (scientific) consistency between guidances. See Ph. Eur. 5.0, Section 5.9 Polymorphism: "Polymorphism (or crystal polymorphism) is a phenomenon related to the solid state; it is the ability of a compound to exist in different crystalline forms having the same chemical composition. Substances that exist in a non-crystalline solid state are said to be amorphous."
II. C. 1.	108	It is misleading to state that (only) large differences in solubility are likely to affect bioavailability. It is also feasible that solubility differences may have greater impact in a modified release form that for the immediate release forms that have been the subject of published studies on the impact of drug solid state differences.	Aguiar and Zelmer (J Pharm Sci (1969) 58 (8) 983-987) Dissolution Behavior of Polymorphs of Chloramphenicol Palmitate and Mefenamic Acid) demonstrated that polymorphs of Chloramphenicol Palmitate with saturation solubilities that were not dramatically different (0.1 and 0.4mg/ml) gave tenfold differences in blood levels in humans.
III. C. 1.	116-121	There is an over reliance on dissolution testing and that it is a surrogate to morphology testing. The draft guidance notes that "inadvertent changes to polymorphic form.....can often be detected by drug product dissolution testing." . What is the recommendation for establishing the correlation between the morphological characteristics for a defined polymorph versus the exhibited dissolution for that polymorph (i.e. morphological testing vs. dissolution testing) to confirm that dissolution testing is in fact the appropriate surrogate?	Dissolution testing is not a substitute for characterization of the solid state form. The text assumes an IVIV correlation and that BA is not dissolution-rate limited, but does not fully recognize other situations, for example where different solid state forms may lead to different product performance.
III. C. 3.	155-164	Monitoring of solid state form is part of assessing the drug product stability.	Amend the wording in line 161 to: "...can have on the chemical and physical stability of drug product." Delete the sentence in lines 161-164
IV.	179	It is incorrect to state that USP monographs generally define identity by chemical name, structure, description etc at the beginning of the monograph. USP monographs invariably stipulate a test for identity, usually infra red spectrum. Such a test may control the solid state form and needs to be included in the text here.	A test identifying the solid state form has to be part of any demonstration of "sameness" so that identical standards apply to all drugs regardless of source.

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IV.	184-192	Given the potential impact of solid state form on product performance, it is inappropriate to argue in scientific terms that polymorphic forms do not render drug substances different.	The statements to the effect that "differences in drug substance solid state form do not render drug substances different active ingredients" flies in the face of established science and sets a dangerous precedent with respect to quality standards for drugs and medications. The pharmaceutical literature is replete with examples where different solid state forms exhibit differing quality-related behaviors. Ignoring the possibility that solid state differences can influence product safety and efficacy sets a very dangerous precedent.
V.	216-218	The recommendation to "...still consider the influence polymorphic forms have on the ability to manufacture the drug product and on the stability of the drug product." is too weak.	Remove the words (in line 218) ".we recommend that you still consider" and add the words "needs to be understood" to the end of line 220.
V. A.	231-233	The emphasis that information on polymorphs can be largely sourced from published work (with a weak 'in some cases" qualifier) does not reflect reality. This assumes that all relevant information is in the public domain and does not therefore take account of the possibility of previously undetected forms.	Many organizations do not publish proprietary information on their materials and pharmacopoeias (on the draft guidance's own admission) may not contain useful evidence. If information in the public domain is incomplete, and if a screening program for the generic product is little more than cursory the possibility exists that novel solid state forms generated by process stresses or drug-excipient interactions, specific to the generic product (e.g. where the product form or process differs from the RLD) will not be detected. Any dissolution test will not have been validated to assess performance of the hitherto unknown form (such validation would require knowledge of the existence of the new solid state form and a proactive study to devise appropriate conditions to assess performance). Reword lines 231 to 233; "ANDA applicants are expected to understand the thermodynamic and kinetic stability of drug substance polymorphs. Information on polymorphism can come from polymorph screening, or in some cases, the scientific literature, patents, compendia or other references."
V. C.	249-250	The statement "...we recommend that you use caution if a metastable form is used." is too weak.	Lines 249 to 250 should be reworded to: "However, since manufacturing processes can affect the polymorphic form, a metastable form should only be used with a full understanding of its thermodynamic and kinetic stability."

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Attachment 1	260-261	The question in the first diamond assumes that all possible/potential solid state forms are "known". This may not be the case: There are many examples of unheralded solid state forms being encountered after a compound is commercialized. It is always possible that a previously unknown solid state form is encountered, with behaviors that render it unsuitable. The absence of a suitable test means that the new unsuitable variant will not be detected.	Again, this assumes that all relevant information is in the public domain and does not therefore take account of the possibility of previously undetected forms.
Attachment 1	263-265	The recommendation to "...consider only those polymorphs that are likely to form during manufacture..." is dependant on full knowledge of which those polymorphs are. Also, it assumes that no further polymorphs will appear.	
Attachment 2	267-274	Example in the first box is weak.	Add IR as an example of a polymorph specification in the USP